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=> file medline
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 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

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 substance identification.

=> d que
L1          3323 SEA FILE=MEDLINE ABB=ON  PLU=ON  FACTOR VII+NT/CT
L2         52072 SEA FILE=MEDLINE ABB=ON  PLU=ON  BLOOD COAGULATION DISORDERS+NT
                 /CT
L3           646 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1(L)(TU OR PD OR PK OR
                 AD)/CT
L4         14083 SEA FILE=MEDLINE ABB=ON  PLU=ON  L2(L)(DT OR PC OR TH OR
                 DE)/CT
L5           314 SEA FILE=MEDLINE ABB=ON  PLU=ON  L3 AND L4
L6          1737 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1/MAJ
L7         37776 SEA FILE=MEDLINE ABB=ON  PLU=ON  L2/MAJ
L8           235 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5 AND L6
L9           282 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5 AND L7
L10          210 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8 AND L9
L12          147 SEA FILE=MEDLINE ABB=ON  PLU=ON  L10 AND PY<2001
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since there are so many hits, I limited the search to Medline & displayed old citations 50-100.

=> d ibib abs l12 50-100

L12 ANSWER 50 OF 147 MEDLINE
ACCESSION NUMBER: 1999152653 MEDLINE
DOCUMENT NUMBER: 99152653 PubMed ID: 10028299
TITLE: A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. rFVIIa Study Group.
AUTHOR: Lusher J M; Roberts H R; Davignon G; Joist J H; Smith H; Shapiro A; Laurian Y; Kasper C K; Mannucci P M
CORPORATE SOURCE: Children's Hospital of Michigan, Detroit, USA.
SOURCE: HAEMOPHILIA, **(1998 Nov)** 4 (6) 790-8.
Journal code: 9442916. ISSN: 1351-8216.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990324
Last Updated on STN: 20000303
Entered Medline: 19990309

AB Recombinant factor VIIa (rFVIIa) was developed to provide an improved procoagulant component capable of 'by-passing' inhibitor antibodies in the treatment of haemophilic patients. The primary objective of this study was to compare the efficacy of two dosage regimens of rFVIIa (given intravenously at periodic intervals) in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B with and without inhibitors. The study was designed as a randomized, double-blind, parallel group, international multicenter trial. Patients were randomly allocated to treatment A: 35 mu kg-1 or B: 70 mu kg-1, in blocks of 2. Within each block, one patient was assigned to the 35 mu kg-1 dosing regimen and the other to 70 mu kg-1 dose. One hundred and fifty subjects from 20 sites were screened for this study and 116 had baseline assessments. Of these, 84 were treated on the protocol and 32 were not treated in the study, in most cases because they did not return to the clinic with an eligible bleeding episode. One hundred and seventy-nine bleeding episodes were treated, of which 145 (81%) were acute haemarthroses. Both treatments were efficacious, with 71% having an excellent (59% and 60%) or effective (12% and 11%) response. Overall, the mean and median number of doses given per episode of joint bleeding were 3.1 and 2, respectively. The mean number of doses was 3.1 for the 70 mu kg-1 group and 2.7 for the 35 mu kg-1 group (P value = 0.142). The study concluded that rFVIIa in a dosage of 35 mu kg-1 or 70 mu kg-1 is both safe and reasonably effective in the treatment of joint or muscle haemorrhages in haemophilic patients with inhibitor antibodies to factor VIII or factor IX. It is concluded that the appropriate dose for the treatment of joint and peripheral muscle bleeding in haemophilic patients with inhibitors is 35-70 mu kg-1 given at 2-3 h intervals until haemostasis is achieved.

L12 ANSWER 51 OF 147 MEDLINE
ACCESSION NUMBER: 1999150034 MEDLINE
DOCUMENT NUMBER: 99150034 PubMed ID: 10027707
TITLE: Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention.

AUTHOR: Santagostino E; Gringeri A; Mannucci P M
CORPORATE SOURCE: Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Hospital and University of Milan, Italy.
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, **(1999 Jan)** 104 (1) 22-6.
Journal code: 0372544. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990322

AB To evaluate the feasibility efficaCy and safety of home treatment with recombinant activated factor VII (rFVIIa), 10 inhibitor patients (all haemophiliacs except one acquired post-partum) self-administered up to four doses of 90 microg/kg rFVIIa every 3+/-1 h. The response was rated by the patient as effective (haemorrhage stopped or decreased substantially), partially effective (reduced) or ineffective (unchanged or worsened). 45 haemarthroses and eight haematomas were treated within a median time of 1.0 h (range 0.3-11.9) from the onset of bleeding, with a median of two rFVIIa doses per course (range 1-4). rFVIIa was effective in 42 episodes (79%), partially effective in six (11%) and failed in five (10%). Compared with partially effective and ineffective treatments, effective treatments started earlier (median time: 0.6 v 2.7 h, P=0.02) and required a smaller number of doses (median: 1.5 v 3, P=0.007). The risk of a partially effective or ineffective treatment was smaller for treatments started within 6 h from the onset of bleeding than for those which started later (OR 0.24, 95% CI 0.09-0.63). Mild side-effects were reported only after 3/113 self-infusions (2.6%). Early home treatment with rFVIIa is safe, feasible and effective, inducing and maintaining haemostasis with a small number of doses.

L12 ANSWER 52 OF 147 MEDLINE
ACCESSION NUMBER: 1999099455 MEDLINE
DOCUMENT NUMBER: 99099455 PubMed ID: 9883002
TITLE: Continuous infusion of recombinant factor VIIa in patients with haemophilia and inhibitors. Experience in The Netherlands and Belgium.
AUTHOR: Mauser-Bunschoten E P; de Goede-Bolder A; Wielenga J J; Levi M; Peerlinck K
CORPORATE SOURCE: University Hospital Utrecht, The Netherlands.
SOURCE: NETHERLANDS JOURNAL OF MEDICINE, **(1998 Dec)** 53 (6) 249-55.
Journal code: 0356133. ISSN: 0300-2977.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990209

AB BACKGROUND: Initial clinical experience with recombinant factor VIIa (rVIIa) for treatment of haemophilia patients with inhibitors against factor VIII or IX has been obtained by administration of rVIIa by repeated

intravenous bolus injections. However, continuous infusion of rVIIa may be a more appropriate administration method if prolonged treatment is indicated. METHODS: We have surveyed and analysed the initial experience with continuous infusion of rVIIa in the Netherlands and Belgium. RESULTS: Five hospitals treated 7 haemophilia patients with inhibitors on 9 different occasions (4 bleedings, 5 surgical interventions) by continuous infusion of rVIIa over a total of 59 days. Haemostatic coverage was considered effective in 8 out of 9 cases and partially effective in 1 case. Continuous infusion of rVIIa was aimed at rVIIa target plasma levels of 10 U/ml and a decrease in prothrombin time (PT) of 3 s compared to control levels. This was obtained by an initial bolus injection of 90 micrograms/kg prior to continuous infusion of rVIIa at doses between 30-6 micrograms/kg/h (mean 17.5 micrograms/kg/h). A conventional one-stage factor VII coagulation assay, often used in combination with a PT, was satisfactory in monitoring rVIIa treatment. The additional clinical value of anti-fibrinolytic and anti-thrombophlebitic treatment was unclear. CONCLUSION: In our experience, rVIIa appeared to be efficacious and safe when administered by continuous infusion. Continuous infusion of rVIIa is more convenient than bolus injections or rVIIa, easy to monitor and provides a cost reduction of > 50%. These advantages make continuous infusion an attractive administration method for prolonged treatment with rVIIa.

L12 ANSWER 53 OF 147 MEDLINE
ACCESSION NUMBER: 1999099381 MEDLINE
DOCUMENT NUMBER: 99099381 PubMed ID: 9882928
TITLE: Immune tolerance induction: a role for recombinant activated factor VII (rFVIIa)?.
AUTHOR: Brackmann H H; Effenberger W; Hess L; Schwaab R; Oldenburg J
CORPORATE SOURCE: Haemophilia Centre, Universitat Bonn, Germany.
SOURCE: EUROPEAN JOURNAL OF HAEMATOLOGY. SUPPLEMENTUM, **(1998)** 63 18-23. Ref: 15
Journal code: 8703474. ISSN: 0902-4506.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990128

AB The development of factor VIII (FVIII) and FIX inhibitors is one of the most serious complications of repeated transfusions in patients with haemophilia. Management of patients with haemophilia with inhibitors must be separated into 2 concepts: the control of acute bleeding episodes and, in the long term, the treatment of the inhibitor itself. This paper will discuss both aspects of the management of these patients, focusing in particular on the therapeutic options available for the treatment of bleeding episodes during immune tolerance induction (ITI) therapy. The second part of the paper will review the management and outcomes of 10 patients with severe haemophilia in whom recombinant activated FVII (rFVIIa: NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) has been used to treat bleeding episodes in the Haemophilia Centre at Bonn University; 6 patients were treated with rFVIIa for bleeding episodes while undergoing ITI. The results obtained demonstrate that rFVIIa is a safe and effective treatment for bleeding episodes and haemostatic cover for surgical procedures in patients with inhibitors. Inhibitor titres were not boosted

in patients with haemophilia and inhibitors on treatment with rFVIIa. Therefore, rFVIIa is also a suitable treatment for bleeding episodes or control of haemostasis during surgery in patients prior to initiation of ITI therapy.

L12 ANSWER 54 OF 147 MEDLINE
ACCESSION NUMBER: 1999099379 MEDLINE
DOCUMENT NUMBER: 99099379 PubMed ID: 9882926
TITLE: Approaches towards successful home treatment in patients with inhibitors.
AUTHOR: Ingerslev J; Thykjaer H; Scheibel E
CORPORATE SOURCE: University Hospital Skejby, Department of Clinical Immunology, Aarhus, Denmark.
SOURCE: EUROPEAN JOURNAL OF HAEMATOLOGY. SUPPLEMENTUM, **(1998)** 63 11-4.
Journal code: 8703474. ISSN: 0902-4506.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990128

AB Significant advances have been achieved in prevention of haemophilic disability through prophylactic administration of concentrates and early administration of coagulation factors to control new bleeding episodes, but there is only limited experience with home treatment in haemophilia patients with inhibitors. A home treatment programme using recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) in early intervention against minor bleeds in patients with high responding inhibitors was initiated in Denmark in June 1994. Following careful education and instruction, 2-3 doses each giving 90-100 micrograms/kg bodyweight of rFVIIa were stored in each patient's home. At the onset of a new bleeding episode patients were instructed to inject 1 dose of rFVIIa, and to call the Haemophilia Centre to discuss further management of the episode. If the drug was not completely effective after 1-2 h, a second dose was injected after 3 h. Patients were further instructed to contact us the following day for final efficacy reporting. In total, 7 patients have been enrolled into the study, and to date 114 bleeding episodes have been managed at home with a mean of 2.1 doses per bleed. On 4 occasions, recurrence of bleeding was noted within 24 h. Hospital admission was required in 9 cases, because of a serious injury, insufficient compliance or, in 2 cases, because bleeding required prolonged treatment. Management of these bleeding episodes required a mean of 18 doses. We propose and discuss key criteria for selection of patients for a home treatment programme. The results of this study demonstrate that early intervention in the home setting with rFVIIa is safe and effective in the management of minor bleeding episodes in haemophilia patients with inhibitors.

L12 ANSWER 55 OF 147 MEDLINE
ACCESSION NUMBER: 1999099378 MEDLINE
DOCUMENT NUMBER: 99099378 PubMed ID: 9882925
TITLE: Early treatment with recombinant factor VIIa results in greater efficacy with less product.
AUTHOR: Lusher J M
CORPORATE SOURCE: Children's Hospital of Michigan and Wayne State University School of Medicine, Detroit, USA.
SOURCE: EUROPEAN JOURNAL OF HAEMATOLOGY. SUPPLEMENTUM,

(1998) 63 7-10.
Journal code: 8703474. ISSN: 0902-4506.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990128

AB Early treatment of bleeding episodes in haemophilia patients offers advantages over later treatment, including minimizing the damage caused by the haemorrhage and reducing the amount of product needed to control it. Self-administration at home also offers greater convenience and time and cost savings for both patient and physician. We compared the amount of recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) used in the treatment of peripheral intramuscular haemorrhages in people with haemophilia A and B with inhibitors and in those with acquired haemophilia, in the compassionate use, dose-finding and US home treatment studies. We also compared the response rates in each of the 3 studies. In the compassionate use setting, in which the mean time from onset of bleeding to initiation of treatment with rFVIIa was 5 d, the mean number of doses given per bleeding episode was 13.6, with 63.1% of episodes without compartment syndrome and 73% with tense muscle/compartment syndrome having an excellent or effective response. In the dose-finding study, average time from onset of bleeding to treatment with rFVIIa was 9 h. The average number of doses given was 3.55, and 72% in the high-dose arm were judged to have an excellent or effective response. In the US home treatment study in which bleeding episodes were treated earlier (mean 1.2 h from onset of bleeding), the mean number of doses given was 2.3, and 92% had an effective response to treatment. These findings indicate that early treatment with rFVIIa has a greater success rate, with fewer doses being required. Home treatment results in cost savings, greater convenience, and less morbidity.

L12 ANSWER 56 OF 147 MEDLINE

ACCESSION NUMBER: 1999090570 MEDLINE
DOCUMENT NUMBER: 99090570 PubMed ID: 9873884
TITLE: Development of a subdural vein thrombosis following aggressive factor VII replacement for postnatal intracranial haemorrhage in a homozygous factor VII-deficient infant.
AUTHOR: Worth L L; Hoots W K
CORPORATE SOURCE: Department of Pediatrics, University of Texas M. D. Anderson Cancer Center, Houston, USA.
SOURCE: HAEMOPHILIA, **(1998 Sep)** 4 (5) 757-61.
Journal code: 9442916. ISSN: 1351-8216.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990218

AB Congenital factor VII deficiency is a rare (1:500,000) autosomally recessive coagulopathy with variable expression and high penetration. In infants the most devastating presentation is that of intracranial haemorrhage. An infant is described with severe factor VII deficiency who developed postnatal intracranial haemorrhage. The baby was treated with

factor VII concentrate (ImmunoA.G., Vienna, Austria). Three weeks after the haemorrhage he developed a dural venous sinus thrombosis. Although factor VII-deficient patients may need treatment with factor VII concentrate, this needs to be carefully monitored because of the thrombotic risk.

L12 ANSWER 57 OF 147 MEDLINE
ACCESSION NUMBER: 1999090481 MEDLINE
DOCUMENT NUMBER: 99090481 PubMed ID: 9873795
TITLE: Safety, efficacy and lessons from continuous infusion with rFVIIa. rFVIIa-CI Group.
AUTHOR: Schulman S
CORPORATE SOURCE: Coagulation Unit, Karolinska Hospital, Stockholm, Sweden.. ssc@divmed.ks.se
SOURCE: HAEMOPHILIA, **(1998 Jul)** 4 (4) 564-7. Ref: 13
Journal code: 9442916. ISSN: 1351-8216.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 19990202
Entered Medline: 19990119
AB Continuous infusion with coagulation factor concentrates has only been widely adopted during the last decade and with recombinant activated factor VII (rFVIIa) only during the last 2 years. Still the accumulated number of days on continuous infusion with this product amounts by now to more than one year, 35 patients and 26 surgical procedures. The experience is reviewed here and compared with data from the conventional bolus dose regimen.

L12 ANSWER 58 OF 147 MEDLINE
ACCESSION NUMBER: 1999084505 MEDLINE
DOCUMENT NUMBER: 99084505 PubMed ID: 9869160
TITLE: Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors.
AUTHOR: Key N S; Aledort L M; Beardsley D; Cooper H A; Davignon G; Ewenstein B M; Gilchrist G S; Gill J C; Glader B; Hoots W K; Kisker C T; Lusher J M; Rosenfield C G; Shapiro A D; Smith H; Taft E
CORPORATE SOURCE: Division of Hematology, University of Minnesota Hemophilia Treatment Center, Minneapolis 55455, USA.
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1998 Dec)** 80 (6) 912-8.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990415

AB OBJECTIVE: To assess the safety and efficacy of a fixed dose of recombinant activated factor VII (rFVIIa; NovoSeven) in the home setting for mild to moderately severe joint, muscle; and mucocutaneous bleeding episodes in patients with haemophilia A or B with inhibitors. DESIGN: Multicentre, open-label, single arm, phase III study of one year duration. METHODS; Patients or their caregivers administered up to three doses of rFVIIa (90 microg/kg i.v.) at 3 h intervals within 8 h of the onset of a mild to moderate bleeding episode. Once the subject considered that rFVIIa had been "effective" with regard to haemostasis (after 1-3 injections), one further (maintenance) dose of rFVIIa was administered. RESULTS: Of 60 patients enrolled, 56 experienced at least one bleed, and 46 completed the one year study. 614 of 877 bleeds (70%) were evaluable according to protocol definitions. Haemostasis was rated as "effective" in 92% (566/614) of evaluable bleeds after a mean of 2.2 injections. For successfully treated episodes, the time from onset of bleeding until administration of the first injection was 1.1+/-2.0 h (mean+/-SD). Twenty-four hours after initial successful response, haemostasis was reported as having been maintained in 95% of cases. Efficacy was comparable for muscle, joint and target joint, and mucocutaneous bleeding episodes. In an intent-to-treat analysis of all 877 bleeding events, efficacy outcomes were equivalent to the evaluable bleeds, with an effective response in 88% of treated episodes. Treatment-related adverse events occurred in 32 (3% of all) bleeding episodes and consisted of re-bleeds/new bleeds in more than 50% (18/32) of these events. A single episode of superficial thrombophlebitis was the only thrombotic complication encountered, and there were no patient withdrawals due to adverse events. Development of FVII(a) antibodies could not be detected, and hypersensitivity reactions to rFVIIa were not reported. CONCLUSION: rFVIIa is effective and well tolerated when used in the home setting to treat mild to moderate bleeding episodes in patients with haemophilia A or B with inhibitors.

L12 ANSWER 59 OF 147 MEDLINE
ACCESSION NUMBER: 1999057304 MEDLINE
DOCUMENT NUMBER: 99057304 PubMed ID: 9843170
TITLE: Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery.
AUTHOR: Shapiro A D; Gilchrist G S; Hoots W K; Cooper H A; Gastineau D A
CORPORATE SOURCE: Indiana University Medical Center, Hemophilia Center, Indianapolis 46260, USA.
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1998 Nov)** 80 (5) 773-8.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990413
Last Updated on STN: 19990413
Entered Medline: 19990330

AB Recombinant factor VIIa (rFVIIa: NovoSeven; Novo Nordisk) has proven efficacy in the treatment of haemophilic patients with inhibitors. This prospective, double-blind study compared rFVIIa (35 vs. 90 microg/kg) in the initiation and maintenance of haemostasis during and after elective surgery. Patients with inhibitors (FVIII, n = 26; FIX, n = 3) received

rFVIIa immediately prior to incision; intraoperatively as needed; every 2 h for the first 48 h; and every 2-6 h for the following 3 days. Haemostasis was evaluated during surgery, at 0, 8, 24 and 48 h and 3, 4 and 5 days after wound closure. After day 5, open-label rFVIIa (90 microg/kg) was available for maintenance. Intraoperative haemostasis was achieved in 28/29 patients. All high-dose patients and 12/15 low dose patients had satisfactory haemostasis during the first 48 h. Twenty-three patients (13/14 high dose) successfully completed the study. Although the 35 microg/kg dose is probably sub-optimal for post-operative management, at least in major procedures, rFVIIa 90 microg/kg is an effective first-line option in surgery for patients with inhibitors.

L12 ANSWER 60 OF 147 MEDLINE
ACCESSION NUMBER: 1999034355 MEDLINE
DOCUMENT NUMBER: 99034355 PubMed ID: 9819046
TITLE: Treatment of acute bleeds with recombinant activated factor VII during immune tolerance therapy.
AUTHOR: Petrini P; Klementz G
CORPORATE SOURCE: Department of Paediatrics and Coagulation Disorders, Karolinska Hospital, Stockholm, Sweden.
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, (1998 Mar) 9 Suppl 1 S143-6.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990126

AB In our clinic, five patients with haemophilia A and one patient with haemophilia B and inhibitors have been treated with immune tolerance induction (ITI) since 1995. Bleeding symptoms during this period have been treated with recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark). Four of the six patients did not need rFVIIa during ITI other than for port-a-cath insertions, but two have been treated intensively because of repeated bleeding problems. The first of these developed inhibitors at the age of 2 years after 11 days of exposure to factor VIII (FVIII). He was treated for 40 bleeding episodes before ITI started, and during ITI he was treated another 24 times, including eight treatments for joint bleeds. Treatment was effective for the different types of bleeding episode. However, in spite of repeated treatment for these joint bleeds, he developed two target joints with synovitis (right knee and left elbow). The synovitis only showed signs of regression when inhibitor levels were reduced due to the ITI regimen. The second patient, now 5 years old, has severe haemophilia B. He developed inhibitors and anaphylaxia having received prophylactic treatment from the age of 1 year. He has now received ITI with 120 units/kg body weight per day of FIX for 68 weeks. In the event of trauma and bleeding he is treated promptly with rFVIIa by his parents at home. Treatment is started with 160-180 microg/kg body weight and, if needed, another dose of 90 microg/kg is given after 3 h. During 1996, 35 bleeds or traumas were treated. The total amount of rFVIIa administered to this child was 211.2 mg. All but one joint bleed and all muscle bleeds needed more than one injection. The need for another injection is judged by the parents and the child from clinical signs, such as pain and swelling. Neither of these two boys have shown any signs of thrombosis or disseminated intravascular coagulation. In summary, rFVIIa is a well tolerated and

effective therapy for acute bleeding episodes during ITI. Dosing and intervals can be the same as for patients not on ITI therapy. Early intervention at home can minimize the risk of synovitis.

L12 ANSWER 61 OF 147 MEDLINE
ACCESSION NUMBER: 1999034351 MEDLINE
DOCUMENT NUMBER: 99034351 PubMed ID: 9819042
TITLE: Antigenicity of activated recombinant factor VII followed through nine years of clinical experience.
AUTHOR: Nicolaisen E M
CORPORATE SOURCE: Vessel Wall Biology, Health Care Discovery, Novo Nordisk, Gentofte, Denmark.. emn@novo.dk
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1998 Mar)** 9 Suppl 1 S119-23.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990126

AB Patients treated with activated recombinant factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) were followed for potential antibody formation. The recombinant product was used to control serious and mild-to-moderate bleeds in a hospital environment and mild-to-moderate bleeds at home. The 267 patients included 222 haemophilia A patients, 16 haemophilia B patients, 16 non-haemophilia patients with inhibitors, and 13 factor VII (FVII)-deficient patients. The individual exposure ranged from one to 121 episodes treated over a period of up to 6 years. Analysis for FVII antibodies in an immunoassay revealed that pre-treatment samples from 5% of the haemophilia A patients had values above the normal range. None of these reactions were specific. Increased post-treatment values were observed in two FVII-deficient patients; both patients had been previously treated with plasma-derived FVII. The FVII-specific antibodies reacted equally well with plasma FVII and rFVIIa. The overall result from antibody determination shows no indication of antibody formation against rFVIIa in haemophilia A or B patients or in non-haemophilia patients with acquired inhibitors; however, FVII-deficient patients represent a risk group for development of antibodies against FVII.

L12 ANSWER 62 OF 147 MEDLINE
ACCESSION NUMBER: 1999034350 MEDLINE
DOCUMENT NUMBER: 99034350 PubMed ID: 9819041
TITLE: Clinical experience with activated factor VII: focus on safety aspects.
AUTHOR: Roberts H R
CORPORATE SOURCE: University of North Carolina School of Medicine, Division of Hematology/Oncology, Chapel Hill 27599-7035, USA.. hrr@med.unc.edu
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1998 Mar)** 9 Suppl 1 S115-8.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209

Last Updated on STN: 19990209
Entered Medline: 19990126

AB Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) has been used extensively worldwide for the treatment of haemophilic patients who have inhibitors to either factor VIII (FVIII) or FIX as well as other miscellaneous conditions. Over 1500 bleeding episodes have been treated with rFVIIa, and various surgical procedures have also been carried out under cover of this product. With the exception of one patient who had FVII deficiency, no antibodies to FVII have been detected. Serious adverse events in patients have been minimal: it is estimated that less than 1% of patients have had a serious adverse event that was possibly related to infusion of rFVIIa. Analysis of these events on a case-by-case basis suggests that rFVIIa is a very safe product with very few side effects. In particular, thromboembolic complications have occurred rarely, if at all.

L12 ANSWER 63 OF 147 MEDLINE
ACCESSION NUMBER: 1999034346 MEDLINE
DOCUMENT NUMBER: 99034346 PubMed ID: 9819037
TITLE: Experiences with continuous infusion of recombinant activated factor VII.
AUTHOR: Schulman S; d'Oiron R; Martinowitz U; Pasi J; Briquel M E; Mauser-Bunschoten E; Morfini M; Ritchie B; Goudemand J; Lloyd J; McPherson J; Negrier C; Peerlinck K; Petrini P; Tusell J
CORPORATE SOURCE: Department of Medicine, Karolinska Hospital, Stockholm, Sweden.. ssc@divmed.ks.se
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1998 Mar)** 9 Suppl 1 S97-101.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990126

AB A questionnaire was sent to 28 haemophilia treatment centres known to have used recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark), to collect data on continuous infusion of this product. This mode of administration was recently introduced for rFVIIa but there are several questions which remain to be answered in order to optimize this technique. Of the 26 responding centres, 14 had used rFVIIa in continuous infusion for 40 treatment episodes over a total of 283 days. In most of the cases the treatment was targeted at a factor VII level of 10 IU/ml, monitored by the one-stage clotting assay. This seemed to be adequate for most of the haemorrhagic and surgical procedures. Pretreatment pharmacokinetic evaluation was performed in only a minority of the cases but is probably of great importance given the wide variation observed in the clearance values. A strategy was necessary to prevent local thrombophlebitis, at least for infusions in peripheral veins; parallel infusion of heparin, saline or dextrose-saline proved effective. The question of optimal monitoring needs further attention. Haemorrhagic complications were significantly less frequent when treatment was combined with the antifibrinolytic tranexamic acid.

L12 ANSWER 64 OF 147 MEDLINE
ACCESSION NUMBER: 1999034345 MEDLINE
DOCUMENT NUMBER: 99034345 PubMed ID: 9819036
TITLE: Safety, efficacy and cost-effectiveness of home therapy with recombinant activated factor VII in a patient with severe haemophilia A and an anti-factor VIII inhibitor.
AUTHOR: Stewart A J; Hanley J P; Ludlam C A
CORPORATE SOURCE: Department of Haematology, Royal Infirmary of Edinburgh, UK.
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1998 Mar)** 9 Suppl 1 S93-5.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990126

AB We report the use of recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) in a patient with severe haemophilia A and a high-titre anti-factor VIII inhibitor. A home therapy protocol was devised and its cost and efficacy were assessed after 2 years. rFVIIa (90 microg/kg) was self-administered at the onset of symptoms of bleeding. Doses were subsequently repeated at 2-h intervals until adequate haemostasis was achieved. The patient experienced a total of 25 bleeding episodes over the 2-year period, of which 23 were treated with up to three doses of rFVIIa. On two occasions, there was a recurrence of bleeding in the same area within 24 h, necessitating retreatment. There was a reduction in the number of inpatient hospital days compared with the 2 years before the use of rFVIIa and, overall, the cost of rFVIIa treatment was less than that of the previously used activated prothrombin complex concentrate (FEIBA; Immuno Ltd, Vienna, Austria). Our experience suggests that in selected haemophiliacs with inhibitors, home treatment with rFVIIa may be safe and cost-effective.

L12 ANSWER 65 OF 147 MEDLINE
ACCESSION NUMBER: 1999034339 MEDLINE
DOCUMENT NUMBER: 99034339 PubMed ID: 9819030
TITLE: Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII.
AUTHOR: Hoffman M; Monroe D M 3rd; Roberts H R
CORPORATE SOURCE: Department of Pathology, Durham Veterans Affairs Medical Center, NC 27705, USA.. maureane@med.unc.edu
CONTRACT NUMBER: HL48320 (NHLBI)
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1998 Mar)** 9 Suppl 1 S61-5. Ref: 13
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990126

AB High levels of recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) have been found to be effective in providing haemostasis in haemophiliacs and in normal individuals with acquired inhibitors to factor VIII (FVIII) or FIX. However, the mechanism of this therapeutic effect of FVIIa is unclear. Opinion is divided over whether high-dose FVIIa therapy works primarily by a tissue factor (TF)-dependent or -independent mechanism. Our group originally favoured a TF-dependent mechanism; however, we have recently found that, at levels comparable with those attained therapeutically, FVIIa activates enough FX on activated platelets to restore platelet surface thrombin generation. These data now lead us to favour a primarily (although not necessarily exclusively) TF-independent mechanism for the haemostatic effect of high-dose FVIIa. We believe that a platelet surface localization of FVIIa activity explains both its safety and efficacy, as well as its haemostatic effect in patients with thrombocytopenia and platelet function defects. Localization on activated platelets would tend to restrict the activity of FVIIa to sites of injury. Activation of FX on the platelet surface in haemophiliacs would provide FXa in a favourable location to escape inhibition by plasma protease inhibitors and be incorporated into platelet prothrombinase complexes. Activation of FIX and FX on platelet surfaces in thrombocytopenia would result in more thrombin generation per platelet, possibly leading to formation of a stable fibrin network even in the absence of an optimal initial platelet plug.

L12 ANSWER 66 OF 147 MEDLINE
ACCESSION NUMBER: 1999022961 MEDLINE
DOCUMENT NUMBER: 99022961 PubMed ID: 10187041
TITLE: Clinical use of recombinant FVIIa (rFVIIa).
AUTHOR: Hedner U; Ingerslev J
CORPORATE SOURCE: Novo Nordisk A/S, Vessel Wall Biology, Gentofte, Denmark.
SOURCE: TRANSFUSION SCIENCE, **(1998 Jun)** 19 (2) 163-76.
Ref: 59
Journal code: 9001514. ISSN: 0955-3886.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Health Technology
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 20010223
Last Updated on STN: 20010223
Entered Medline: 19981210

AB Haemostasis is initiated by the complex formed by TF and FVIIa present in the blood (1% of the FVII protein). Recombinant FVIIa, which is active only after having formed complex with TF exposed following tissue damage, has been demonstrated to induce haemostasis in haemophilia patients with life- and limb-threatening bleedings with an efficacy rate of 76-84% in patients having failed on other treatment. Several had proven septicaemia but only one patient developed consumption coagulaopathy during extensive surgical manipulation and removal of myonecrotic tissue. No antibody formation against FVII has been seen in haemophilia patients. In 13 major surgical episodes complete intra- and post-operative haemostasis was achieved. rFVIIa has been used successfully in FVII-deficient patients and has been found to normalise the PT in patients with liver disease and in warfarin treated individuals. Single patients with platelet defects and with vWillebrand's disease type 3 achieved haemostasis with rFVIIa.

L12 ANSWER 67 OF 147 MEDLINE
ACCESSION NUMBER: 1999011105 MEDLINE

DOCUMENT NUMBER: 99011105 PubMed ID: 9797081
TITLE: Severe acquired hemophilia A successfully treated with activated recombinant human factor VII.
AUTHOR: Papadaki H A; Xylouri I; Valatas W; Petinarakis J; Kontopoulou I; Eliopoulos G D
CORPORATE SOURCE: Department of Hematology, University of Crete School of Medicine, University Hospital of Heraklion, Greece.
SOURCE: ANNALS OF HEMATOLOGY, **(1998 Sep)** 77 (3) 123-5.
Journal code: 9107334. ISSN: 0939-5555.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981112

AB A case of acquired hemophilia A in a 65-year-old woman is presented. The patient had been subjected to cholecystectomy 2 months before the bleeding tendency appeared. On admission, she had easy bruising and prolonged activated partial thromboplastin time, but during hospitalization she had severe hemorrhage into the right gluteal and femoral muscles. An inhibitor of the factor VIII coagulant protein (FVIII:C) of high Bethesda titer was found in her serum. The patient was successfully treated with activated recombinant human factor VII (rhFVIIa) and immunosuppression. We conclude that rhFVIIa is a safe, effective, and fast-acting preparation for the treatment of severe hemorrhage in patients with acquired hemophilia A, and that the simultaneous administration of azathioprine and corticosteroids may suppress production of the inhibitor.

L12 ANSWER 68 OF 147 MEDLINE
ACCESSION NUMBER: 1999006394 MEDLINE
DOCUMENT NUMBER: 99006394 PubMed ID: 9789965
TITLE: [Recombinant activated factor VII: a new treatment for hemophilia].
Le facteur VII active recombinant: un nouveau traitement de l'hemophilie.
AUTHOR: Goudemand J
CORPORATE SOURCE: Laboratoire d'hematologie, Centre hospitalier regional et universitaire de Lille, hopital Claude-Huriez, France.
SOURCE: TRANSFUSION CLINIQUE ET BIOLOGIQUE, **(1998 Aug)** 5 (4) 260-5. Ref: 15
Journal code: 9423846. ISSN: 1246-7820.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981208

AB Recombinant factor VIIa (NovoSeven, NovoNordisk) initiates coagulation in inhibitor patients who either develop alloantibodies to clotting factors or those with acquired haemophilia. The human gene for FVII was transfected into a baby hamster kidney (BHK) cell line which secretes FVII in a single-chain form. Recombinant FVII is purified from the medium by four chromatographic steps including immunoaffinity chromatography with a monoclonal anti-FVII. During this process rFVII undergoes autoactivation

to rFVIIa. NovoSeven does not contain any stabilising protein including human albumin. The SA is 50 KU/mg, the concentration is 0.6 mg/mL. Recovery is 45%, clearance is 31 mL/h/kg, the half-life was estimated between 2 and 3 hours. Combined to tissue factor rFVIIa directly activates factor X without implication of FVIIIa and FIXa. There is no systemic coagulation activation. Efficacy was assessed from data derived largely from the Compassionate Use Programme and clinical studies using rFVIIa as first line therapy. Various situations were proven to be efficiently resolved with rFVIIa including surgeries. Usual dosages are 90-120 mcg/kg administered every 2-3 hours. There were no side effects even in cases of prolonged administration. Drawbacks are the short half-life and the cost of the product.

L12 ANSWER 69 OF 147 MEDLINE
ACCESSION NUMBER: 1998448794 MEDLINE
DOCUMENT NUMBER: 98448794 PubMed ID: 9775655
TITLE: [New possibilities in the management of hemorrhagic diathesis caused by factor deficiency and thrombocytopenia: recombinant active factor VII concentrate].
Uj lehetoseg a faktorhianyos, az antitest okozta es a thrombocyta eredetu verzekenyseg kezeleseben: a rekombinans aktiv VII-es faktor koncentratum.
AUTHOR: Udvardy M
CORPORATE SOURCE: Debreceni Orvostudomanyi Egyetem, II. Belgyogyaszati Klinika.
SOURCE: ORVOSI HETILAP, **(1998 Sep 20)** 139 (38) 2255-8.
Journal code: 0376412. ISSN: 0030-6002.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Hungarian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 19990129
Entered Medline: 19981022
AB Recombinant Factor VIIa, a new therapeutic tool to treat severe bleeding caused by inhibitory haemophilia cases, some cases of thrombocytopenia and thrombocytopathy (e.g. severe type III von Willebrand disease) receives growing attention in clinical practice. Exogeneous FVIIa-in a supraphysiological concentration (clearly over 6 U/ml) seems to be able to generate quickly and safely (without thrombotic side effects) thrombin--the final enzyme of clotting--in physiological, or pathological conditions. A concise review about the possible mechanisms of action, indications, monitoring and clinical experience gained sofar with FVIIa is given in this report.

L12 ANSWER 70 OF 147 MEDLINE
ACCESSION NUMBER: 1998380031 MEDLINE
DOCUMENT NUMBER: 98380031 PubMed ID: 9716174
TITLE: Treatment of a patient with Bernard-Soulier syndrome and recurrent nosebleeds with recombinant factor VIIa.
AUTHOR: Peters M; Heijboer H
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1998 Aug)** 80 (2) 352.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981204

L12 ANSWER 71 OF 147 MEDLINE
ACCESSION NUMBER: 1998353122 MEDLINE
DOCUMENT NUMBER: 98353122 PubMed ID: 9690812
TITLE: The use of recombinant activated factor VII in congenital and acquired factor VII deficiencies.
COMMENT: Comment in: Blood Coagul Fibrinolysis. 1999 Dec;10(8):521-2
AUTHOR: Muleo G; Santoro R; Iannaccaro P G; Papaleo P; Leo F
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1998 Jun)** 9 (4) 389-90.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 20000512
Entered Medline: 19981021

L12 ANSWER 72 OF 147 MEDLINE
ACCESSION NUMBER: 1998084411 MEDLINE
DOCUMENT NUMBER: 98084411 PubMed ID: 9423795
TITLE: The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study.
AUTHOR: Hay C R; Negrier C; Ludlam C A
CORPORATE SOURCE: University Dept. of Haematology, Manchester Royal Infirmary, UK.. Haemophilia@Man.Ac.UK
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1997 Dec)** 78 (6) 1463-7.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19990129
Entered Medline: 19980212

AB Recombinant factor VIIa was used to treat 38 patients with acquired haemophilia participating in the Novoseven compassionate-use program. 19 were male, median age 59, range 2-89 years. The median pre-treatment anti-human (H) and anti-porcine (P) inhibitor titre was H 43 BU/ml (range 1-4500) and P 4.5 BU/ml (range 0-1600). Recombinant factor VIIIa was used as first-line therapy for 14 bleeding episodes and as salvage-therapy for 60 episodes which failed to respond to blood-product therapy given for a median of four days (range 1-21 days) prior to treatment with rVIIa. Pre-rVIIa treatment was not reported for four episodes. The indications for treatment were 7 haemarthroses, 40 muscle haematomas, 20 urinary or GI haemorrhages and 3 surgical interventions. The median starting dose of rVIIa was 90.4 microg/kg (range 45-181). A median of 28 doses (range 1-541) were given per episode, over a median 3.9 days (range 0-43). Efficacy was assessed clinically 8 and 24 h after the start of rVIIa and at the end of treatment. A good response was obtained in all 14 bleeds for which rVIIIa was used as first-line therapy. The response after 24 h

of rVIIa salvage-therapy for 60 bleeds was good in 75%, partial in 17% and poor in 8%. Efficacy was unreported in 4 cases. The median prothrombin time (PTT) shortened from 12 s (range 9.3-20) pre-treatment to 8.8 s (range 6-14) during treatment. The clinical response did not correlate with the dose of rVIIa used, the type of bleed or the degree of shortening of the PTT following rVIIa infusion. Three patients died from haemorrhagic complications of acquired haemophilia. This mortality of 7.9% is lower than previously reported for this condition. Although one patient developed DIC during treatment with rVIIa, this was probably attributable to hypovolaemic shock, massive transfusion and the use of PCCs. This study demonstrates that rVIIa is a safe, useful and effective treatment for bleeding in patients with acquired haemophilia.

L12 ANSWER 73 OF 147 MEDLINE
ACCESSION NUMBER: 1998030268 MEDLINE
DOCUMENT NUMBER: 98030268 PubMed ID: 9364986
TITLE: Effects of plasma kallikrein specific inhibitor and active-site blocked factor VIIa on the pulmonary vascular injury induced by endotoxin in rats.
AUTHOR: Uchiba M; Okajima K; Murakami K; Okabe H; Okamoto S; Okada Y
CORPORATE SOURCE: Department of Medicine, Kumamoto University School of Medicine, Japan.
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1997 Oct)** 78 (4) 1209-14.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 20000303
Entered Medline: 19980112

AB The acute respiratory distress syndrome (ARDS) is a serious complication of sepsis. To evaluate the role of the coagulation system in the pathogenesis of ARDS in sepsis, we examined the effects of the administration of a synthetic plasma kallikrein specific inhibitor (PKSI) and of active-site blocked factor VIIa (DEGR-VIIa) on the pulmonary vascular injury induced by E. coli endotoxin (ET) in rats. Administration of PKSI prevented the pulmonary vascular injury induced by ET as well as pulmonary histological changes in animals administered ET, but it did not affect the intravascular coagulation. The opposite effect was seen with DEGR-VIIa, which prevented the intravascular coagulation but not the pulmonary vascular injury. PKSI did not inhibit the activation of the complement system induced by ET leading to the activation of neutrophils. Findings suggest that PKSI may prevent the pulmonary vascular injury induced by ET by inhibiting kallikrein, which activates the neutrophils. The intrinsic pathway of coagulation may be more important than the extrinsic pathway in the pulmonary vascular injury produced by ET.

L12 ANSWER 74 OF 147 MEDLINE
ACCESSION NUMBER: 97465468 MEDLINE
DOCUMENT NUMBER: 97465468 PubMed ID: 9326188
TITLE: Severe aquired haemophilia A treated with recombinant factor VIIa.
AUTHOR: Shafi T; Jeha M T; Black L; Al Douri M
CORPORATE SOURCE: Department of Pathology, Riyadh Armed Forces Hospital, Saudi Arabia.
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, **(1997 Sep)** 98 (4)

910-2.
Journal code: 0372544. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19990129
Entered Medline: 19971209

AB Acquired haemophilia can be associated with various conditions including pregnancy, autoimmune diseases and lymphoproliferative disorders, though often no underlying cause is found. It often presents with a rapid onset of muscle bleeding and involves the IgG antibody. It may be treated with human or porcine factor VIII (FVIII), prothrombin complex concentrates, factor IX (FIX) complex concentrates, factor VIIa (FVIIa) or by immunosuppression. We report a case of acquired haemophilia in a 40-year-old woman diagnosed following laparotomy. She was treated unsuccessfully using human FVIII and cryoprecipitate, porcine FVIII and FIX complex concentrate, before being treated with recombinant FVIIa (NovoSeven, Novo-Nordisk). On treatment with recombinant FVIIa, bleeding stopped rapidly with no side-effects and the abdominal haematoma was evacuated with minimal post-operative bleeding.

L12 ANSWER 75 OF 147 MEDLINE
ACCESSION NUMBER: 97343194 MEDLINE
DOCUMENT NUMBER: 97343194 PubMed ID: 9199823
TITLE: Successful short-term oral surgery prophylaxis with rFVIIa in severe congenital factor VII deficiency.
AUTHOR: Billio A; Pescosta N; Rosanelli C; Amaddii G; Fontanella F; Coser P
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1997 Jun)** 8 (4) 249-50.
Journal code: 9102551. ISSN: 0957-5235.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 19970916
Entered Medline: 19970904

L12 ANSWER 76 OF 147 MEDLINE
ACCESSION NUMBER: 97181759 MEDLINE
DOCUMENT NUMBER: 97181759 PubMed ID: 9053631
TITLE: [Recombinant factor VIIa. A new alternative for patients with hemophilia].
Rekombinant faktor VIIa. Nytt alternativ for hemofilipatienter.
AUTHOR: Tengborn L
CORPORATE SOURCE: Koagulations-centrum, Sahlgrenska sjukhuset, Goteborg.
SOURCE: LAKARTIDNINGEN, **(1997 Jan 15)** 94 (3) 140-2. Ref: 22
Journal code: 0027707. ISSN: 0023-7205.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Swedish

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19990129
Entered Medline: 19970310

L12 ANSWER 77 OF 147 MEDLINE
ACCESSION NUMBER: 97064314 MEDLINE
DOCUMENT NUMBER: 97064314 PubMed ID: 10184611
TITLE: Recombinant factor VIIa (r-FVIIa) in haemophilia management.
AUTHOR: Rice K M; Savidge G F
CORPORATE SOURCE: St Thomas' Hospital, London, U.K.
SOURCE: TRANSFUSION SCIENCE, **(1996 Sep)** 17 (3) 339-40.
Journal code: 9001514. ISSN: 0955-3886.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Health Technology
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 20010223
Last Updated on STN: 20010223
Entered Medline: 19961218

L12 ANSWER 78 OF 147 MEDLINE
ACCESSION NUMBER: 97059871 MEDLINE
DOCUMENT NUMBER: 97059871 PubMed ID: 8904192
TITLE: Treatment of factor VII deficiency with recombinant factor VIIa.
AUTHOR: Bauer K A
CORPORATE SOURCE: Hematology-Oncology Section, Department of Medicine, Brockton-West Roxbury, Harvard Medical School, Boston, Masschusetts, USA.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 155-8. Ref: 22
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB Factor VII deficiency is a relatively infrequent hereditary bleeding disorder. Recombinant factor VIIa has been used to treat patients with factor VII deficiency with bleeding episodes or undergoing surgery. The drug has shown a high efficacy rate and will provide factor VII-deficient patients with a therapeutic agent that is not derived from human plasma.

L12 ANSWER 79 OF 147 MEDLINE
ACCESSION NUMBER: 97059870 MEDLINE
DOCUMENT NUMBER: 97059870 PubMed ID: 8904191
TITLE: Use of recombinant factor VIIa (NovoSeven) in the treatment of two patients with type III von Willebrand's disease and an inhibitor against von Willebrand factor.
AUTHOR: Ciavarella N; Schiavoni M; Valenzano E; Mangini F; Inchingolo F
CORPORATE SOURCE: Servizio di Coagulazione, Centro Emofilia,

Policlinico-Universita, Bari, Italy.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 150-4.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB Two siblings affected by type III von Willebrand's disease with precipitating alloantibodies against von Willebrand's factor (vWF) and not susceptible to treatment with factor VIII/vWF concentrates received recombinant activated factor VII for oral surgery. This therapy, combined with antifibrinolytic drugs and local application of fibrin glue, seems to be effective and safe. It may be considered a promising approach to the management of this rare condition.

L12 ANSWER 80 OF 147 MEDLINE
ACCESSION NUMBER: 97059869 MEDLINE
DOCUMENT NUMBER: 97059869 PubMed ID: 8904190
TITLE: American experience with home use of NovoSeven: recombinant factor VIIa in hemophiliacs with inhibitors.
AUTHOR: Shapiro A D
CORPORATE SOURCE: The James Whitcomb Riley Hospital for Children, Indiana University Medical Center, Indianapolis, USA.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 143-9.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB A novel investigational product, recombinant factor VIIa, manufactured by Novo Nordisk, is presently in clinical trial for evaluation of safety and efficacy when used in the home setting in patients with hemophilia A and B with inhibitors for control of hemostasis in mild to moderate joint, muscle and mucocutaneous bleeding episodes. The clinical trial is an open label, multicenter, uncontrolled study in which 60 patients are enrolled and treated for 1 year with the goal of accumulating 120 evaluable bleeding episodes. Reported here is an outline of the study, review of currently enrolled patient demographics, and the data accumulated to date from the Indiana Hemophilia Comprehensive Center.

L12 ANSWER 81 OF 147 MEDLINE
ACCESSION NUMBER: 97059868 MEDLINE
DOCUMENT NUMBER: 97059868 PubMed ID: 8904189
TITLE: Thrombelastgram as a hemostatic monitor during recombinant factor VIIa treatment in hemophilia A patients with inhibitor to factor VIII.
AUTHOR: Yoshioka A; Nishio K; Shima M
CORPORATE SOURCE: Department of Pediatrics, Nara Medical University, Japan.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 139-42.

Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB Thrombelastgram (TEG) is an old but automated instrument that demonstrates changes occurring during blood coagulation and fibrinolysis. TEG was evaluated to be better than activated partial thromboplastin time (APTT) as a monitor of hemostatic effects when using recombinant factor VIIa (65-80 mu g/kg) in 3 hemophilia A patients with a high titer of factor VIII inhibitors. TEG was more suitable than APTT, because r, r + k and ma values of TEG were normalized at least for 4 h after the infusion, whereas APTT was variably shortened and was not always maintained at a normal level for 4 h.

L12 ANSWER 82 OF 147 MEDLINE
ACCESSION NUMBER: 97059867 MEDLINE
DOCUMENT NUMBER: 97059867 PubMed ID: 8904188
TITLE: Recombinant factor VIIa in joint and muscle bleeding episodes.
AUTHOR: Bech R M
CORPORATE SOURCE: Novo Nordisk, Gentofte, Denmark.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 135-8.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB Recombinant factor VIIa (rFVIIa) improves haemostasis and eliminates the risk of transmission of blood-borne infection in haemophilia patients with inhibitors, acquired inhibitors to factor VIII or IX or FVII deficiency. rFVIIa has been available on a compassionate use basis since 1988 and has been administered to 111 patients for a total of 494 joint and muscle bleeding episodes. Seventy-nine percent of joint and 65% of muscle bleeding episodes were evaluated by the investigator as having an excellent/effective response. rFVIIa is also an effective treatment for joint and muscle bleeding episodes in patients undergoing immune tolerance regimens and does not affect the inhibitor titre level.

L12 ANSWER 83 OF 147 MEDLINE
ACCESSION NUMBER: 97059866 MEDLINE
DOCUMENT NUMBER: 97059866 PubMed ID: 8904187
TITLE: NovoSeven (recombinant factor VIIa) in centeral nervous systems bleeds.
AUTHOR: Rice K M; Savidge G F
CORPORATE SOURCE: Haemophilia Reference Centre, St. Thomas' Hospital, London, UK.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 131-4.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB Data is presented from two compassionate-use clinical trials using recombinant factor VIIa (rFVIIa) to treat central nervous system haemorrhage in 18 haemophilia A and B patients with inhibitors, and in 3 patients with FVII deficiency. Prior to rFVIIa treatment 78% of the haemophilia patients had inhibitor titres greater than 10 Bethesda units/ml. Sixty-two percent of the bleeding episodes were treated with a mean dose of 80-100 mu g/kg of rFVIIa administered repeatedly until cessation of bleeding. The overall efficacy was 84% with only one fatality and there were no major adverse events or laboratory indicators of disseminated intravascular coagulation.

L12 ANSWER 84 OF 147 MEDLINE
ACCESSION NUMBER: 97059864 MEDLINE
DOCUMENT NUMBER: 97059864 PubMed ID: 8904185
TITLE: Major surgery in haemophilic patients with inhibitors using recombinant factor VIIa.
AUTHOR: Ingerslev J; Freidman D; Gastineau D; Gilchrist G; Johnsson H; Lucas G; McPherson J; Preston E; Scheibel E; Shuman M
CORPORATE SOURCE: Coagulation Laboratory and Haemophilia Centre, University Hospital Aarhus/Skejby, Denmark.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 118-23.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB In the haemophilic patient, development of antibodies that inhibit the function of the missing coagulation factor causes several delicate problems. Most importantly, antibodies will block the function of the specific coagulation factor, and often the antibody activity is so fierce that effective substitution therapy is outruled. In consequence, alternative measures must be adopted to control bleeding. Amongst those most commonly employed, like factor IX concentrates, activated prothrombin complex concentrates, and factor VIII of porcine origin, a new recombinant activated factor VII molecule has been evaluated clinically for some years with promising results. The aim of the present paper was to present a series of patients suffering from haemophilia A or B in whom inhibitors have complicated the clinical picture, and in whom a surgical procedure was indicated. As part of a compassionate use program devised by the producer of this genetically engineered factor VIIa, 12 patients underwent life-saving or essential surgery where the recombinant factor VIIa product was used to promote haemostasis in 13 surgical procedures. Due to a short in vivo half-life of activated factor VIIa, frequent administration was scheduled, injecting factor VIIa every 2-3 h for up to 2 days after which dosage intervals were prolonged. In one case, a global evaluation of the end treatment result was not reported, but in all of the other 12 cases the end result were considered excellent (n = 11) or efficient (n = 1). In none of the cases was other types of coagulation factor treatment modalities necessary. In conclusion, recombinant factor VIIa seems a tempting alternative to traditional treatment of the haemophilic patient

with inhibitors, in whom surgery is called for. With other types of haemostatic agents, surgery in haemophilic inhibitor patients has only been studied rarely, and operations have generally been restricted to life-threatening situations.

L12 ANSWER 85 OF 147 MEDLINE
ACCESSION NUMBER: 97059863 MEDLINE
DOCUMENT NUMBER: 97059863 PubMed ID: 8904184
TITLE: Experience with recombinant factor VIIa in Australia and New Zealand.
AUTHOR: McPherson J; Teague L; Lloyd J; Jupe D; Rowell J; Ockelford P; Ekert H; Street A; Faase A; Hedner U
CORPORATE SOURCE: Haemophilia Treatment Centres, Mater Hospital, Newcastle, Australia.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 109-17.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB Recombinant factor VIIa (rFVIIa; NovoSeventrademark) was availablefor compassionate use in Australia and New Zealand from 1991 to 1994. Over this period there were 18 treatment episodes in 9 patients, age 8-66 years, with haemophilia A and high titre inhibitors cross-reacting with porcine factor VIII. There were no significant adverse effects. Treatment with rFVIIa resulted in a successful outcome in 8 potentially life-threatening (retroperitoneal, subdural, gastro-intestinal) bleeds. Elective cystoscopy, repair of a cranial flap, yttrium synovectomy and inguinal herniotomy were performed successfully, as was surgical decompression of a flexor pollicis longus bleed. Treatment of a patient with an infected haematoma had limited success, attributed to intermittent suboptimal doses. In 2 patients, satisfactory haemostasis was achieved for multiple dental extractions; subsequent oozing was attributed to suboptimal rFVIIa and/or antifibrinolytic therapy.

L12 ANSWER 86 OF 147 MEDLINE
ACCESSION NUMBER: 97059862 MEDLINE
DOCUMENT NUMBER: 97059862 PubMed ID: 8904183
TITLE: Dosing and monitoring NovoSeven treatment.
AUTHOR: Hedner U
CORPORATE SOURCE: Novo Nordisk, Gentofte, Denmark.
SOURCE: HAEMOSTASIS, **(1996)** 26 Suppl 1 102-8.
Journal code: 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20021030
Entered Medline: 19970219

AB The concept of using factor VIIa (FVIIa) to induce hemostasis in hemophilia is new and takes advantage of the normal tissue factor/FVII-dependent coagulation pathway which is enhanced by the administration of extra exogenous recombinant FVIIa. Since this is a pharmacological treatment and not a simple substitution therapy the

current dosis recommendations are based on preclinical data (in vitro and in animals) as well as on clinical experience. It is concluded that the initial dose should be high enough to maintain a plasma level of FVII-coagulant activity (FVII:C) at > 6 U/ml for several hours corresponding roughly to a dose of 90-120 mu g/kg.

L12 ANSWER 87 OF 147 MEDLINE
ACCESSION NUMBER: 97019100 MEDLINE
DOCUMENT NUMBER: 97019100 PubMed ID: 8865715
TITLE: Intraoperative use of plasma-derived activated factor VII (F VII a) in a hemophilia A patient with inhibitors.
AUTHOR: Matsuyama K; Ushijima K; Kano T; Tsuchiya H
CORPORATE SOURCE: Department of Anesthesiology, Kumamoto University School of Medicine.
SOURCE: MASUI. JAPANESE JOURNAL OF ANESTHESIOLOGY, **(1996 Feb)** 45 (2) 235-8.
Journal code: 0413707. ISSN: 0021-4892.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19990129
Entered Medline: 19961212

AB We treated a 1-year 9-month-old boy with severe hemophilia A who developed high level of F VIII inhibitor. A placement of an implantable intravenous access device was scheduled under general anesthesia. After a slow induction using oxygen, nitrous oxide and sevoflurane, a peripheral venous line was placed and plasma-derived F VII a was infused. A catheter was inserted via the jugular vein to the SVC and it was connected to the device placed subcutaneously in his right chest wall. The peroperative blood loss was slight, and anesthesia and surgery went uneventfully.

L12 ANSWER 88 OF 147 MEDLINE
ACCESSION NUMBER: 97018915 MEDLINE
DOCUMENT NUMBER: 97018915 PubMed ID: 8865531
TITLE: Immunological aspects of recombinant factor VIIa (rFVIIa) in clinical use.
AUTHOR: Nicolaisen E M; Hansen L L; Poulsen F; Glazer S; Hedner U
CORPORATE SOURCE: Novo Nordisk A/S, Gentofte, Denmark.
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1996 Aug)** 76 (2) 200-4.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19990129
Entered Medline: 19970115

AB Patients, receiving rFVIIa for treatment of bleeding disorders, have been followed for specific antibody formation. No antibodies against FVII were demonstrated in 170 patients, with hemophilia, or with acquired inhibitors to clotting factors. Of 6 FVII-deficient patients, one overdosed patient developed antibodies to human FVII. There was no indication of de novo formation of antibodies to potential contaminating foreign protein, which could be correlated to the rFVIIa treatment. Except for the FVII-deficient population, which may represent a risk group, rFVIIa

appears to be immunologically safe for use in patient groups with bleeding disorders, including hemophilia A and B patients.

L12 ANSWER 89 OF 147 MEDLINE
ACCESSION NUMBER: 97003714 MEDLINE
DOCUMENT NUMBER: 97003714 PubMed ID: 8851025
TITLE: Clinical update on the use of recombinant factor VII.
AUTHOR: Glazer S; Hedner U; Falch J F
CORPORATE SOURCE: Biopharmaceuticals Division, Novo Nordisk A/S, Gentofte, Denmark.
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, **(1995)** 386 163-74. Ref: 40
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19990129
Entered Medline: 19961210

L12 ANSWER 90 OF 147 MEDLINE
ACCESSION NUMBER: 96419896 MEDLINE
DOCUMENT NUMBER: 96419896 PubMed ID: 8822604
TITLE: A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa.
AUTHOR: Tengborn L; Petruson B
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1996 Jun)** 75 (6) 981-2.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970407
Last Updated on STN: 19970407
Entered Medline: 19970325

L12 ANSWER 91 OF 147 MEDLINE
ACCESSION NUMBER: 96393733 MEDLINE
DOCUMENT NUMBER: 96393733 PubMed ID: 8800506
TITLE: Recombinant clotting factor concentrates.
AUTHOR: Lusher J M
CORPORATE SOURCE: Wayne State University School of Medicine, MI, USA.
SOURCE: BAILLIERES CLINICAL HAEMATOLOGY, **(1996 Jun)** 9 (2) 291-303. Ref: 51
Journal code: 8800474. ISSN: 0950-3536.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19990129

Entered Medline: 19970210

L12 ANSWER 92 OF 147 MEDLINE
ACCESSION NUMBER: 96276529 MEDLINE
DOCUMENT NUMBER: 96276529 PubMed ID: 8701403
TITLE: Feasibility of using recombinant factor VIIa in continuous infusion.
AUTHOR: Schulman S; Bech Jensen M; Varon D; Keller N; Gitel S; Horoszowski H; Heim M; Martinowitz U
CORPORATE SOURCE: National Hemophilia Center, Chilm Sheba Medical Center, Tel-Hashomer, Israel.
SOURCE: THROMBOSIS AND HAEMOSTASIS, **(1996 Mar)** 75 (3) 432-6.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 19990129
Entered Medline: 19960905

AB Recombinant factor VIIa (rFVIIa; NovoSeven) is a recent addition to the hemostatic alternatives for the treatment of hemophiliacs with inhibitors. A drawback in the use of rFVIIa has been its half-life of only about 2 h, which necessitates very frequent and punctual injections. We evaluated the stability of reconstituted, but not further diluted, rFVIIa in 3 infusion systems (WalkMed 350 and CADD-Plus minipumps and Meddex 2001 syringe pump). The factor VII (F VII) activity was maintained for at least 3 days at room temperature with only a minor and clinically insignificant increase in oxidized forms of rFVIIa and minimal leaching of the plastic softeners dibutylphthalate and di-octylphthalate after 24-48 h. Addition of heparin, 5-10 U/ml, to reconstituted rFVIIa caused a loss of about 50% of the activity within 4 h of storage in the infusion system, whereas low molecular weight heparin had no such effect. Repeated samples showed that the infusion systems maintained sterility. Reconstituted rFVIIa did not support bacterial growth when inoculated with Staphylococcus aureus or Escherichia coli to any greater extent than did reconstituted factor VIII, lidocaine in saline or heparin in saline. Two patients were treated with continuous infusion of rFVIIa on 4 occasions (total knee arthroplasty, wound revision, and twice straightening of a 90 degrees contracture of the knee under general anaesthesia). A preoperative pharmacokinetic evaluation was performed, and the clearance was used to calculate the maintenance dose, aiming at a FVII level of 10 U/ml, which proved to be a hemostatic level. The first patient had no change in the clearance during the two treatment episodes. He suffered from repeated thrombophlebitis at the infusion site. The second patient had a progressive decrease of the clearance from 86.4 to 24.7 ml/h/kg. He received during the first treatment a parallel infusion with heparin (approximately 250 U/24 h) to the same venous access and did not develop thrombophlebitis during 3.5 days of therapy. For the second episode low molecular weight heparin was added directly to the infusion bag, and no adverse effects were observed. Continuous infusion with rFVIIa is thus feasible with the minipumps used by us, eliminates the need for 2 h injections and reduces the total dose of rFVIIa by 50-75%, depending on the behaviour of the clearance.

L12 ANSWER 93 OF 147 MEDLINE
ACCESSION NUMBER: 96224564 MEDLINE
DOCUMENT NUMBER: 96224564 PubMed ID: 8668070

TITLE: Recombinant factor VII.
COMMENT: Comment on: Med J Malaysia. 1995 Jun;50(2):166-70
AUTHOR: Ng S C
SOURCE: MEDICAL JOURNAL OF MALAYSIA, **(1995 Dec)** 50 (4) 425.
Journal code: 0361547. ISSN: 0300-5283.
PUB. COUNTRY: Malaysia
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 19990129
Entered Medline: 19960806

L12 ANSWER 94 OF 147 MEDLINE
ACCESSION NUMBER: 96194502 MEDLINE
DOCUMENT NUMBER: 96194502 PubMed ID: 8616058
TITLE: rVIIa therapy to secure haemostasis during central line insertion in children with high-responding FVIII inhibitors.
AUTHOR: Smith O P; Hann I M
CORPORATE SOURCE: Institute of Child Health, London, England.
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, **(1996 Mar)** 92 (4) 1002-4.
Journal code: 0372544. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960620
Last Updated on STN: 19990129
Entered Medline: 19960612

AB The provision of adequate haemostasis in children with haemophilia A (HA) who have developed high-responding inhibitors continues to be a great challenge to haematologists and institutional resources. The most exciting development in the management of acute bleeding in these patients, irrespective of inhibitor titre, has been the use of recombinant activated factor VII (rVIIa). Three severe HA children with high-responding inhibitors underwent four central line insertions (two Hickman catheters and two port-a-caths, one replaced because of infection) with rFVIIa cover to enable continuous FVIII infusions. No adverse haemorrhagic events occurred and immune tolerance therapy (ITT) using high-dose FVIII therapy was initiated and inhibitor eradication was achieved in al three patients at 8, 10 and 7 months. A further patient who had a central line in situ prior to the development of a high-responding inhibitor was also successfully 'tolerized' at 6 months using the same protocol. Interestingly, all four patients had the IVS 22 mutation.

L12 ANSWER 95 OF 147 MEDLINE
ACCESSION NUMBER: 96080246 MEDLINE
DOCUMENT NUMBER: 96080246 PubMed ID: 7485101
TITLE: Prophylaxis and therapy with factor VII concentrate (human) immuno, vapor heated in patients with congenital factor VII deficiency: a summary of case reports.
AUTHOR: Cohen L J; McWilliams N B; Neuberg R; Zinkham W; Bauer K; Gribble T J; Glowalla M B; Borson R; Phillips M D; Kunschak

M
CORPORATE SOURCE: Maine Children's Cancer Program, Maine Medical Center, Portland, USA.
SOURCE: AMERICAN JOURNAL OF HEMATOLOGY, **(1995 Dec)** 50 (4) 269-76.
Journal code: 7610369. ISSN: 0361-8609.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951228

AB Hereditary factor VII deficiency is a rare autosomal recessive condition, usually associated with normal or reduced levels of a functionally defective molecule. The available means of treating this condition in North America presents serious health risks to the patient. Transfusion with fresh frozen plasma carries a risk of volume overload and a significant risk for viral transmission. Sustained prothrombin complex therapy is associated with a high risk for thrombogenic complications. This communication describes the use of Factor VII Concentrate (Human) Immuno, Vapor Heated--an intermediate purity factor VII concentrate from Immuno A.G.--for the treatment of 13 patients with factor VII deficiency. Treatment regimens described include those for long-term prophylaxis (three children), acute hemorrhages (two children, one adult), peripartum prophylaxis (one patient), and surgical coverage (two children, four adults). Prophylaxis and therapy were successful in all cases, the medication was well-tolerated, and there were no complications. In the three cases of long-term prophylaxis in children, doses of 10-50 IU/kg were given one to three times a week; one patient has undergone long-term prophylaxis for approximately 8 years, one patient for 1 year, and one patient for 1 1/2 years. Three cases in which Factor VII Concentrate was principally used for treatment of acute episodes of bleeding are described. One infant received Factor VII Concentrate on about 50 occasions for treatment of mucosal bleeding; a correction to 40-100% resulted in cessation of bleeding within 15 min in all cases. For treatment of an episode of intracranial bleeding, an 8-year-old boy received a dose of 37 IU/kg Factor VII Concentrate every 6 hr for peak factor VII levels of approximately 100% and troughs as low as 4% over the 11-day treatment period. A 37-year-old adult male with intracranial bleeding received alternating doses of 16 IU/kg and 8 IU/kg every 6 hr for 10 days with peak factor VII levels in the upper thirties (%). The peak favor VII level during surgical coverage with Factor VII Concentrate (neurosurgery, open reduction of ankle bones, dental surgery, pituitary adenoma surgery, closed liver biopsy) was approximately 100% in all cases, with trough levels ranging from 8 to 65% over treatment periods of 24 hr to 16 days using treatment intervals of 6-12 hr.

L12 ANSWER 96 OF 147 MEDLINE
ACCESSION NUMBER: 95329573 MEDLINE
DOCUMENT NUMBER: 95329573 PubMed ID: 7605877
TITLE: The use of recombinant factor VIIa in a patient with acquired haemophilia A undergoing surgery.
AUTHOR: Doughty H A; Northeast A; Sklair L; Roques T; Young A E; Savidge G F; Hunt B J
CORPORATE SOURCE: Haemophilia Centre, St Thomas' Hospital, London, UK.
SOURCE: BLOOD COAGULATION AND FIBRINOLYSIS, **(1995 Apr)** 6 (2) 125-8.
Journal code: 9102551. ISSN: 0957-5235.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828
Last Updated on STN: 19990129
Entered Medline: 19950817

AB An elderly woman with acquired haemophilia A secondary to a monoclonal gammopathy, required elective surgery for a parotid tumour but was unable to tolerate conventional treatment. Recombinant activated factor VII (rVIIa) was used successfully to cover a biopsy and then subsequent resection of the tumour. The use of rVIIa in the management of acquired inhibitors is discussed.

L12 ANSWER 97 OF 147 MEDLINE
ACCESSION NUMBER: 95199656 MEDLINE
DOCUMENT NUMBER: 95199656 PubMed ID: 7892567
TITLE: [Recombinant activated Factor VII (Novoseven Novo Nordisk) for hemostasis in acquired Factor VIII-inhibitor hemophilia].
Rekombinanter aktivierter Faktor VII (Novoseven Novo Nordisk) zur Blutstillung bei erworbener Hemmkorper-Hamophilie.
AUTHOR: Meili E O; Dazzi H; von Felten A
CORPORATE SOURCE: Departement fur Innere Medizin, Universitatsspital Zurich.
SOURCE: SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. JOURNAL SUISSE DE MEDECINE, **(1995 Mar 4)** 125 (9) 405-11.
Journal code: 0404401. ISSN: 0036-7672.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950427
Last Updated on STN: 19990129
Entered Medline: 19950417

AB One life threatening mediastinal hemorrhage and two limb threatening hemorrhages, one in the retroperitoneal and thigh muscles and the other in the back of the hand requiring surgical evacuation, were treated with recombinant activated factor VII concentrate (rFVIIa; Novoseven Novo Nordisk) in a patient with a postpartum acquired inhibitor against factor VIII. High dose activated prothrombin complex concentrate (Feiba sTIM4 Immuno), repeatedly administered, had proven to be ineffective; porcine factor VIII concentrate (Hyate C Porton) had become ineffective due to a rise in inhibitor titers against human and porcine factor VIII as well. 90 micrograms rFVIIa per kg body weight was administered as an i.v. bolus injection every 2-3.5 hours. The treatment periods were 22.5 days in the mediastinal and 11 days in each of the two other hemorrhages. Hemostasis was promptly achieved and maintained. All manipulations (bone marrow biopsy, surgical evacuation of the hematoma, change of venous access, withdrawal of drains, change of dressings) were done immediately after rFVIIa administration, without bleeding complications. There were no side effects despite the high dose, frequent and long lasting treatment with a total of 234 x 4.8 and 46 x 3.6 mg rFVIIa. The concentrate was well tolerated, there were no signs of systemic activation of coagulation, either in the coagulation test results or clinically, in spite of patient's factor VII levels up to 60 U/mL and prothrombin times around 6 s. No inhibitors against patient's factor VII, induced by rFVIIa, were detected. Due to its extrinsic factor VIII bypass effect, rFVIIa led to

excellent hemostasis even with inhibitor titers of 376 Bethesda units against human and 44 against porcine factor VIII. Nevertheless, immunosuppressive treatment with cyclophosphamide and prednisone was performed, with prompt decrease of the inhibitor titer.(ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 98 OF 147 MEDLINE
ACCESSION NUMBER: 95184275 MEDLINE
DOCUMENT NUMBER: 95184275 PubMed ID: 7878711
TITLE: Low risk of viral infection after administration of vapor-heated factor VII concentrate or factor IX complex in first-time recipients of blood components. International Factor Safety Study Group.
AUTHOR: Shapiro A; Abe T; Aledort L M; Anderle K; Hilgartner M W; Kunschak M; Preston F E; Rivard G E; Schimpf K
CORPORATE SOURCE: James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis.
SOURCE: TRANSFUSION, **(1995 Mar)** 35 (3) 204-8.
Journal code: 0417360. ISSN: 0041-1132.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950419
Last Updated on STN: 19990129
Entered Medline: 19950331

AB BACKGROUND: Vapor-heated human factor VII concentrate and human factor IX complex are both obtained from prothrombin complex, undergo similar methods of manufacture, and are subjected to an identical two-step vapor-heating process for virus inactivation. STUDY DESIGN AND METHODS: Intermediate-purity vapor-heated human factor VII concentrate and vapor-heated human factor IX complex were monitored for safety with regard to viral infection in the context of an International Factor Safety Study, a prospective study that follows the revised recommendations from the International Congress of Thrombosis and Hemostasis (ICTH). Because the rarity of the respective hereditary deficiencies would have made separate analyses unrealizable, the results were combined for the final analysis. Entry required that patients have no history of transfusion with any blood derivative. After the first infusion of the study drug, patients were monitored for 6 months for the development of non-A, non-B hepatitis (NANBH) and infection with hepatitis B virus (HBV) and for 15 months for infection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV). An event was defined as a positive result on any test for any infection. An alanine aminotransferase level more than 2.5 times the upper limit of normal on two consecutive occasions was defined as an event for NANBH. HBV infection was monitored with tests for three different HBV markers: the HBV surface antigen, antibody against the HBV surface antigen, and antibody against HBV core antigen. HCV and HIV infection were monitored with tests for HCV and HIV antibodies. RESULTS: The 25 patients who completed the study (1 has not completed the study and 1 dropped out) received a total of 434 infusions comprising 17 different production lots of the concentrates. Twenty patients were analyzable for NANBH and 25 for HCV and HIV infection. Since most patients had been given HBV vaccination, only 4 patients were analyzable for this end point. None of the patients showed evidence of having developed an event. These data satisfy ICTH criteria when the products are considered together, but vapor-heated factor VII concentrate does not qualify alone because there

were only five patients in this group. CONCLUSION: Vapor-heated factor VII concentrate and vapor-heated factor IX complex are associated with a low risk of viral infection. Preliminary results are also presented, indicating that the concentrates are safe with regard to inhibitor development.

L12 ANSWER 99 OF 147 MEDLINE
ACCESSION NUMBER: 95026044 MEDLINE
DOCUMENT NUMBER: 95026044 PubMed ID: 7939777
TITLE: The clinical use of factor VIIa in the treatment of factor VIII inhibitor patients.
AUTHOR: Seremetis S V
CORPORATE SOURCE: Mount Sinai Medical Center, New York, NY 10029-6574.
SOURCE: SEMINARS IN HEMATOLOGY, **(1994 Apr)** 31 (2 Suppl 4) 53-5.
Journal code: 0404514. ISSN: 0037-1963.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19990129
Entered Medline: 19941118

L12 ANSWER 100 OF 147 MEDLINE
ACCESSION NUMBER: 94317642 MEDLINE
DOCUMENT NUMBER: 94317642 PubMed ID: 8042614
TITLE: Recombinant activated factor VII (rFVIIa) therapy for intracranial hemorrhage in hemophilia A patients with inhibitors.
AUTHOR: Schmidt M L; Gamerman S; Smith H E; Scott J P; DiMichele D M
CORPORATE SOURCE: Division of Pediatric Hematology/Oncology, University of Illinois Medical School, Chicago.
SOURCE: AMERICAN JOURNAL OF HEMATOLOGY, **(1994 Sep)** 47 (1) 36-40.
Journal code: 7610369. ISSN: 0361-8609.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940905
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AB We report the use of recombinant VIIa (rFVIIa) in the treatment of five ICHs in two factor VIII-deficient patients with inhibitors. In four of five ICHs, rFVIIa was the only factor replacement used at doses of 60-135 micrograms/kg every 2-4 hr for 12-14 days. Hemostasis at the primary site of bleeding was achieved in all cases, and all patients survived with no permanent neurologic deficits. However, the patient who received the highest dose of rFVIIa during the first 4 days of therapy developed clinical symptoms consistent with a cerebral vascular accident of the brainstem characterized by acute onset of truncal ataxia and upward-gaze nystagmus on day 8 of rFVIIa therapy. While receiving rFVIIa therapy for treatment of these five ICHs, four treatment courses were complicated by

bleeding at sites other than the primary site, including two episodes of localized oozing at central line insertion sites, two episodes of hemarthrosis, and two episodes of epistaxis. Antifibrinolytic therapy with tranexamic acid was effective in two of these episodes. Laboratory evaluation revealed shortening of the PT, variable shortening without normalization of the APTT, peak factor VII activity levels 7-30-fold higher than normal baseline values, and normal antithrombin III (ATIII) and alpha 2-antiplasmin levels. In four of five ICHs, there was a 20-40% decrease in fibrinogen levels from baseline. The decrease in fibrinogen was accompanied by an increase in fibrin degradation products in 3/5 episodes and a 15-35% decrease in plasminogen activity levels in 2/5 episodes. Tissue factor pathway inhibitor (TFPI) levels remained stable and in the normal range. Although rFVIIa is an effective new therapy for the treatment of ICH in hemophilia patients with inhibitors, its optimal use with respect to safety and efficacy requires further clinical study.